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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,506	01/12/2001	Charlotte Kensil	106941.190	2171

7590 04/20/2004

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,506	KENSIL, CHARLOTTE	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,33-38,40 and 44-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,33-38,40 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/30/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 31, 33-38, 40 and 44-46 are pending in the application.

This Office Action is in response to the Amendment filed on 12/30/03.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/30/03 has been entered.

Response to Amendment

The rejection of claims 31, 33-38, 40 and 44 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

Claims 31, 33-38, 40, 44 and newly added claims 45 and 46 stand rejected under 35 U.S.C. 112 1st paragraph for reasons set forth of the record mailed on 7/2/03 and further discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 33-38, 40, 44 and newly added claims 45 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to this argument, Applicant argues that the specification enables the claimed invention to its full scope because it teaches 1) a composition comprising substantially purified saponin, QS-21, in the absence of a vaccine antigen, with or without CpG oligo, can stimulate innate immunity; 2) innate immunity plays an important role in the protective response to cancer; 3) agents that safely stimulate innate immunity can be used as therapeutic agents against cancer; 4) type of cancers can be treated by the present invention. Applicant further submitted a declaration which presents *in vivo* data that support the efficacy of the use of saponin for treatment of cancer, and conclude that one of skilled in the art can readily follow the teachings of the specification to use saponin to stimulate innate immunity, thereby treat cancer. Applicant thus concludes that the claimed invention is fully sported by the instant specification.

These arguments have been fully considered but deemed unpersuasive. As discussed in the previous office action, the state of art at the time of filing teaches that *Quillaja saponaria* saponin can potentiate innate immune response and is useful as vaccine adjuvant. The prior art also teach that saponins isolated from different source possess different chemical structures which affect their biological activity (see Rao and Sung, 1995). Although some saponins such as soybean saponins have been reported to have anti-carcinogenic activity in cell culture and mice models, there is no report to date that they are clinically effective in treating cancer. Further, there is no report that *Quillaja saponaria* saponin has anti-tumor activity. The specification only teaches that a method of stimulate an innate immune response in a mouse by using saponins

isolated from *Quillaja saponaria*. As such, whether administering *Quillaja saponaria* saponin to an individual can treat cancer is unpredictable. The specification only prophetically states that the innate immunity plays an important role in the protective response to cancer. It fails to establish whether the enhancement of the innate immunity exerted by QS21 is sufficient to provide a therapeutic effect to a cancer. As such, the nexus between treating cancer and increase in innate immune response is missing. Thus, one skilled in the art would have to engage in undue experimentation to practice the method as claimed.

The prior art teaches that carcinogenesis is a step-wise process which is caused by accumulation of multiple somatic mutations in a cell's DNA (see Lynch et al., 2002). With each step along the process, more mutations are acquired until malignant transformation has occurred. Common mutational events observed in human cancers include point mutation, altered DNA methylation, gene rearrangements, amplifications, and deletions, which result in either gain of function, loss of function and epigenetic alteration that lead to both aberrant gene expression and silencing (see page 777, 2nd paragraph). Leon et al. (2002) also point out that most human malignancies are resulted from several factors which contribute to cancer development, and that it is often difficult to find a single causative agent fully responsible for the disease (see page 59 1st paragraph). As such, the prior art regard the success of using a single agent such as a composition comprising a *Quillaja saponaria* saponin for the treatment of any type of cancer is unpredictable.

The claims are further drawn to a method of treating cancer by using any type of *Quillaja saponaria* saponin in either modified or unmodified forms. As discussed above, the prior art teaches that different chemical structures of saponin affect their biological activity (see Rao and

Sung, 1995, page 718S, 1st col., 4th paragraph, lines 5-7). The specification only teaches QS21 enhances innate immune response. As such, whether administering any type of *Quillaja saponaria* saponin can treat cancer is unpredictable.

The Kensil declaration has been fully considered. The declaration demonstrates that intratumoral injection of QS21 slow down the tumor growth in BALB/c mouse inoculated with Meth A fibrosarcoma. The declaration further demonstrates that administering QS21 in the vicinity of tumor site before and after inoculation of P815 tumor cells in DBA mouse inhibited tumor development in the mice. Applicant thus conclude that the declaration provide sufficient enablement for a method of treating any type of cancer by administering *Quillaja saponaria* saponin with any type of structural modification. The Examiner respectively disagrees with this conclusion. As discussed above, the prior art regard treating cancer as unpredictable. Moreover, in an article published in Science (1997), the author indicate that animal systems for identifying new drugs are often faulty, especially the xenograft model for testing anticancer drugs (see page 1041, 1st col., 3rd paragraph). The animals with transplanted human tumors do not handle drugs as the human body does. In using immuno-deficient mouse models, the mouse cannot reject the foreign tissue, the tumors usually grow unchecked and behave differently to tumors naturally occurring in human. For such reasons, a compound that is effective in xenograft model is often works poorly in human (see page 1041, 2nd col., last paragraph). The data shown by the declaration is from a xenograft mouse tumor model. One cannot predict whether QS21 would work effectively in human because tumor originated in human behave very differently than that developed after inoculation of tumor cells in a mouse. As such, based solely on the data provided in the declaration, it does not overcome the art-recognized unpredictability in treating a

cancer. Furthermore, the declaration does not teach whether other structurally modified *Quillaja saponaria* saponin can treat any type of cancer. Therefore, the declaration does not provide sufficient teaching to enable the instantly claimed invention. As such, one skilled in the art would have to engage in undue experimentation to practice the invention. The rejection is thus maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.